Atty. Docket No. EFFR0010U-US

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: McCallister et al. : Confirmation No.:8537

: GROUP ART UNIT: 1617

APPLICATION NO: 10/092,083 :

FILED: March 6, 2002 : EXAMINER: Jiang, S. A.

FOR: Effervescent Compositions Comprising Bisphosphonates and Methods Related Thereto

Second Declaration under 37 CFR §1.132

COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

SIR:

I, Marshall A. Hayward, Ph.D., hereby make the following declaration:

1. I am the same Marshall A. Hayward, Ph.D. who previously prepared a 37 CFR §1.132 Declaration for the above-identified application, executed on 15 December 2003, and filed on 16 December 2003.
2. Under my direction, a human bioavailability and bioequivalence clinical trial was conducted to show the bioequivalence between EX101, a highly buffered effervescent formulation containing 70 mg of alendronate (ALN), and commercial 70 mg Fosamax tablets from Merck & Co. The results of that study are presented in Table 3 below.

3. Furthermore, in order to show that highly buffered effervescent formulations improve the absorption characteristics and dosing consistency of ALN compared to conventional effervescent formulations, such as those taught in Katdare (U.S. 5,853,759; "Katdare"), I have analyzed data published in a study conducted by Merck & Co. and submitted to the FDA as part of a New Drug Application (NDA). The results of that Merck NDA study are available to the public in redacted form under the Freedom of Information Act, a copy of which is attached to this Declaration. Pertinent data from it are presented in Table 2 below.

4. Thus, four dosage forms are involved – (1) EX101 (70 mg ALN), (2) the Merck effervescent formulation, which in my opinion is representative of Katdare (10 mg ALN) because the buffering levels are similar to the examples in Katdare (confirmed to me by confidential communications with Merck & Co.), and (3) Fosamax tablets (70 mg and 10 mg, respectively) corresponding in dosages to the effervescent formulations in each test. In the actual studies, the two effervescent forms were compared only to their corresponding tablet form, not to each other. Also, the Merck ALN absorption study was conducted over a period of 36 hours while the EX101 absorption was conducted over 48 hours. These differences do not affect my conclusions.

5. In both the Merck effervescent study and our own EX101 study, alendronate concentration was measured in urine rather than blood, because there is no valid blood assay for ALN. Thus, the pharmacokinetic parameters described below refer to ALN measured in urine collected over various time periods.

6. As reported in Table 2, the EX101 (70 mg alendronate) study establishes its bioequivalence with Fosamax tablets on a potency corrected basis. For instance, the mean (average) time to maximal drug absorption (Tmax) is statistically the same for EX101 as for Fosamax tablets. Also, the mean (average) concentration maximum (Cmax) is statistically the same for EX101 as for Fosamax tablets.

7. It is desirable for a dosing form to be as consistent and predictable as possible. The data show that EX101 is a superior formulation to Fosamax tablets because

the tablets have a more extreme of range of absorption (lower minimal absorption and higher maximal absorption), and most importantly, because alendronate absorption from Fosamax tablets shows a significantly higher coefficient of variation (CV) with respect to the mean absorption level. In other words, drug absorption from the EX101 formulation shows lower variability than the corresponding tablet.

8. In the Merck effervescent study (10 mg alendronate), the buffering capacity of the formulation was far lower than in EX101. While the CV of the Merck effervescent was also improved over its corresponding tablet, the CV of the Merck effervescent formulation was significantly higher than that of EX101.

9. The results for CV are brought together in Table 1. Merck reports a least squares mean and standard deviation per their ANOVA; it is therefore appropriate to use our geometric mean and coefficient of variation. The Merck CV is calculated from data on page 12 of the NDA (Treatment E) as follows: SD/LS = 21.3/25.9 = 82 %. The Merck study was reported in ug, not ng. I have put everything in terms of ng in the tables below.

10. **Table 1:** Coefficients of variation (CV) of EX101 vs. Merck's Effervescent form

Parameter	EX101	Merck Effervescent 10 mg tablet reference	Comment
Mean Alendronate Absorption Coefficient of variation (CV)%	57%	82%	EX101 shows significantly less variation then Merck's effervescent form

11. This comparison in Table 1 shows that the highly buffered EX101 provides a much improved coefficient of variation compared to the Merck effervescent, i.e.,

57% vs 82%. The coefficient of variation is a measure of variability, hence our formulation demonstrates significantly less variability.

12. **Table 2:** Merck 10 mg effervescent form vs. Fosamax 10 mg tablet

Parameter	Merck 10 mg Merck effervescent form	Fosamax 10 mg tablet reference	Comment
Alendronate absorption, ng, as Least Squares Mean +/- SD*, Merck study	25,900 +/- 21,300	26,100 +/- 36,500	
Coefficient of variation, % (least squares mean)	82%	140%	See page 12 of Merck NDA (Treatment E) SD/LS = 21.3/25.9 = 82 %)
*SD, standard deviation of the mean			

13. **Table 3:** Alendronate absorption from EX101 vs. Fosamax tablets.

Parameter	EX101	Fosamax Tablets	Comment
Bioequivalence Point Estimate	89.18%	(100%)	Potency adjusted EX101 absorption point estimate expressed as a % of Fosamax tablets. Dosage forms are bioequivalent.
Bioequivalence, 90% confidence interval Lower Limit	82.72%		EX101 expressed as a % of Fosamax. Meets criteria for bioequivalance; dosage forms are bioequivalent.
Bioequivalence, 90% confidence interval Upper Limit	96.14%		EX101 expressed as a % of Fosamax. Meets criteria for bioequivalance; Dosage forms are bioequivalent.

Elimination mean Cmax +/- SD (ng/ml)	65,569 +/- 34,934	78,155+/- 55,649	No statistical difference. Meets criteria for bioequivalance; Dosage forms are bioequivalent.
Elimination mean Tmax +/- SD (hours)	1.46 +/- 0.67	1.28+/- 0.55	No statistical difference. Meets criteria for bioequivalance; Dosage forms are bioequivalent.
Mean Absorption (ng)	206,156	255,817	
(Coefficient of Variation -- least squares mean)	57.0%	69.0%	Higher variability for Fosamax tablets than EX101
Upper Absorption Maximum (ng)	731,508	1,231,499	Much higher for Fosamax and further from the mean
Lower absorption Minimum (ng)	68,597	31,895	Much lower for Fosamax and further from the mean
Alendronate absorption, ng, as Geometric Mean, EX101	181,956	213,659	

14. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: May 30, 2008 By: _____
Marshall A. Hayward, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-575

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	21-575
Submission Dates	November 15, 2002; July 18, 2003; August 25, 2003
Brand Name	FOSAMAX®
Generic Name	alendronate sodium
Reviewer	S.W. Johnny Lau
Team Leader	Hae-Young Ahn
OCPB Division	DPE II (HFD-870)
ORM division	Metabolic and Endocrine (HFD-510)
Sponsor	Merck Research Laboratories
Relevant IND	32,033
Submission Type: Code	original: S
Formulation: Strength(s)	70 mg/75 mL oral solution
Indication	to treat osteoporosis in postmenopausal women and increase bone mass in men with osteoporosis

1 Executive Summary

The sponsor is marketing the 70 mg alendronate oral tablet (FOSAMAX®) for once weekly administration to treat osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis. The sponsor submitted NDA 21-575 on November 15, 2002 to seek approval for the 70 mg alendronate/75 mL oral solution for once weekly administration to claim the same indications as the 70 mg alendronate oral tablet. The oral solution will serve as an alternative to patients who have difficulty swallowing tablets or prefer solution. The sponsor did not conduct any clinical efficacy and safety study for NDA 21-575. However, the sponsor conducted 4 clinical pharmacology studies. Briefly, Studies:

- P110 and P163 are pilot relative bioavailability studies of oral solutions to marketed tablets
- P177 is a pivotal bioequivalence study for the 70 mg/75 mL solution to the 70 mg tablet
- P204 is a rising, single dose study to investigate the tolerability and dose linearity of oral solution doses between 70 mg/75 mL and 375 mg/100 mL

Studies P110 and P163 were not thoroughly reviewed since they were pilot studies to guide the development of an alendronate solution formulation and to determine the intrasubject variability for Study P177's sample size calculation, respectively.

Per Study P177, the geometric mean ratio for the 36-hour cumulative alendronate urinary excretion of the 70 mg solution to the 70 mg tablet was 0.99 and the 90% CI was (0.90 – 1.10) as well as the 95% CI was (0.88 – 1.12). Based on these observations, the 70 mg alendronate/75 mL oral solution is equally bioavailable to the 70 mg alendronate oral tablet. However, bioequivalence could not be adequately assessed because the urine sampling intervals were not short enough (0 - 8, 8 - 24, and 24 - 36 h postdose) to determine the maximum alendronate excretion rate. The tested solution formulation in Study P177 was identical to the to-be-marketed solution formulation. The tested tablet formulation in Study P177 was identical to the marketed tablet formulation.

Per Study P204, dose linearity does not exist between 70 mg/75 mL and 375 mg/100 mL solution based on the 36-hour cumulative alendronate urinary excretion. However, dose linearity appears to exist between 140 mg/75 mL and 375 mg/100 mL solution based on the 36-hour cumulative alendronate urinary excretion.

1.1. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) reviewed the Human Pharmacokinetics and Bioavailability section for NDA 21-575 and finds it acceptable. However, the sponsor should receive the following comment:

- The sponsor should change this statement to "FOSAMAX 70 mg oral [redacted] solution and FOSAMAX 70 mg tablet are equally bioavailable." from " [redacted] in the CLINICAL PHARMACOLOGY/*Absorption* section of the proposed labeling. Bioequivalence could not be adequately assessed because the urine sampling intervals were not short enough to determine the maximum alendronate excretion rate.

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-575 was conducted on August 25, 2003; participants included H. Malinowski, A. Selen, S-M. Huang, T. Kehoe, E. Colman, C. Sahajwalla, S. Haidar, H. Ahn, and J. Lau.

FT signed by Hae-Young Ahn, Ph.D., Team Leader 8/ /03

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2 Table of Contents

3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor developed the 70 mg alendronate/75 mL oral solution to treat osteoporosis in postmenopausal women and to increase bone mass in men with osteoporosis. The sponsor did not conduct any safety and efficacy study for the 70 mg alendronate/75 mL oral solution but conducted a pivotal bioequivalence study (P177) between the 70 mg alendronate oral solution and the 70 mg alendronate oral tablet. The sponsor is marketing the 70 mg alendronate tablet, which has the indications being sought for the 70 mg alendronate oral solution.

Synopses for 2 pilot bioavailability studies (P110 and P163) are in Attachment 1.

Study P177 was a 3-way crossover, fasted, single-dose bioequivalence study between 35 mg/75 mL oral solution, 70mg/75mL oral solution, and 70 mg oral tablet. A washout of at least 12 days existed between doses. Sequential urine samples were collected for 36 hours postdose to determine excreted alendronate. The clinically-tested oral solution formulation was identical to the to-be-marketed oral solution formulation. The clinically-tested oral tablet formulation was identical to the marketed oral tablet formulation. Based on the geometric mean ratio for the 36-hour cumulative alendronate urinary excretion of the 70 mg solution to the 70 mg tablet was 0.99 and the 90% CI was (0.90 – 1.10) as well as the 95% CI was (0.88 – 1.12), the 70 mg alendronate/75 mL oral solution is equally bioavailable to the 70 mg alendronate oral tablet. However, the maximum alendronate urinary excretion rate could not be adequately estimated because of the long urine collection intervals. Based on the geometric mean ratio for the 36-hour cumulative alendronate urinary excretion of the 35 mg solution to the 70 mg tablet was 0.84 and the 90% CI was (0.76 – 0.93) as well as the 95% CI was (0.74 – 0.95), the 35 mg alendronate/75 mL oral solution is not equally bioavailable to the 70 mg alendronate oral tablet.

Study P204 was conducted to examine the single dose tolerability and dose linearity from 70 to 375 mg alendronate oral solutions. Cumulative alendronate urinary excretion 36 hours postdose was determined upon administration at each of the 4 doses: 70 mg/75 mL, 140 mg/75 mL, 280 mg/75 mL, and 375 mg/100 mL. Dose linearity does not exist between 70 mg and 375 mg alendronate doses. However, dose linearity appears to exist between 140 and 375 mg alendronate doses.

4 Question-Based Review

4.1 General Attributes

What is the formulation of the to-be-marketed 70 mg alendronate oral solution?

Alendronate Sodium Oral [redacted] Solution, 70 mg - Market Composition

Ingredients	Reference	Function	mg/mL[3]
Alendronate Sodium[1] *(as anhydrous free acid equivalent)*	Ph. Eur.	[redacted]	[redacted]
Sodium Citrate Dihydrate	USP/Ph. Eur.		
Citric Acid Anhydrous	USP/Ph. Eur.		
Sodium Butylparaben[2,4]	BP		0.07500
Sodium Propylparaben[2,4]	NF/Ph. Eur.		0.2250
Saccharin Sodium	USP/Ph. Eur.		
Artificial Raspberry Flavor			
Purified Water	USP/Ph. Eur.		

1 – Pill volume is targeted to [redacted]
1 – The product is provided as a unit dose. Each bottle contains 91.35 mg of Alendronate Sodium, which is equivalent to 70 mg as an anhydrous free acid.
2 – Alternatively, this antimicrobial preservative may be referred to as Sodium Ethyl Hydroxybenzoate
2 – Alternatively, this antimicrobial preservative may be referred to as Sodium Propyl Hydroxybenzoate
3 – [redacted]

4.2 General Clinical Pharmacology

Alendronate clinical pharmacology information is available in:

- FOSAMAX® product labeling
- A.G. Porras et al. Pharmacokinetics of alendronate. *Clin Pharmacokinet* **36**:315-28 (1999).
- J.H. Lin. Bisphosphonates: a review of their pharmacokinetic properties. *Bone* **18**:75-85 (1996).

4.3 Bioanalytical

Is the bioanalytical method for alendronate properly validated?

Briefly, the alendronate bioanalytical method used in pivotal bioequivalence (BE) study (P177) for human urine samples [redacted]

[redacted]

Validation for the alendronate bioanalytical method in human urine samples for Study P177 follows:

	Alendronate
Method	[redacted]
Lower Limit of Quantitation, ng/mL	[redacted]
Recovery, %	unavailable
Linearity, ng/mL	[redacted]
Accuracy	
intraday	[redacted]
interday	[redacted]
Precision, % CV	
intraday	[redacted]
interday	[redacted]

The alendronate bioanalytical method used in the dose linearity study (P204) for human urine samples

[redacted]

Validation for the alendronate bioanalytical method in human urine samples for Study P204 follows:

	Alendronate
Method	[redacted]
Lower Limit of Quantitation, ng/mL	[redacted]
Recovery, %	unavailable
Linearity, ng/mL	[redacted]
Accuracy	
intraday	[redacted]
interday	[redacted]
Precision, % CV	
intraday	[redacted]
interday	[redacted]

It was concluded that the bioanalytical methods were adequately validated.

4.4 General Biopharmaceutics

1. Does difference exist between the to-be-marketed formulation and the tested formulation in the pivotal BE study?

Per NDA 21-575/N-000-BB on July 18, 2003, the sponsor stated that the 70 mg alendronate oral solution tested in Study P177 was identical to the to-be-marketed 70 mg alendronate oral solution. Moreover, the 70 mg alendronate tablet formulation used in Study P177 (pivotal) was identical to the marketed 70 mg alendronate oral tablet formulation.

2. Is assessment of BE via cumulative alendronate urinary excretion data valid?

Per the Code of Federal Regulations 320.24 (b)(2), the urinary excretion of alendronate data is an acceptable alternative to assess BE since alendronate is not metabolized but renally eliminated.

3. Did the sponsor adequately assess the alendronate BE between the oral solution and oral tablet?

Study P177 is an open-label, randomized, 3-period, fasted, single-dose, crossover study to evaluate the alendronate BE between oral solutions and oral tablet in 108 healthy adult subjects (see details on study design, synopsis, and data analysis in Attachment 2). Briefly, 35 mg alendronate/75 mL solution versus 70 mg alendronate tablet and 70 mg alendronate/75 mL solution versus 70 mg alendronate tablet were assessed for BE. Each subject directly drank the oral solutions from the dosing bottles followed with 60 mL of tap water from a separate cup, whereas each subject received the oral tablet with 250 mL of tap water. A washout of at least 12 days separated the doses. Study P177 was the pivotal BE study.

The sample size of 108 subjects was estimated prior to the start of the study, based upon an observed within-subject standard deviation (SD) for total urinary excretion of 0.50 (on the natural log μg scale).

The 0.5 value was chosen because the observed within-subject SD for total urinary excretion was 0.45 (log μg) for pilot study (P163) comparing the 35 and 70 mg alendronate oral solution to the 70 mg alendronate tablet.

Through the sponsor's SAS transport files submitted on July 18, 2003 (N000BZ), this reviewer calculated the geometric mean ratio (GMR) and 90% CI for the 70 mg solution versus 70 mg tablet and the 35 mg solution versus 70 mg tablet.

Summary statistics to assess BE follows:

70 mg alendronate	GMR	90% CI
solution vs. tablet	0.9945	0.8987 – 1.100
(mg) alendronate	GMR	90% CI
(35) solution vs. (70) tablet	0.8378	0.7563 – 0.9282

Based on these observations, the 70 mg alendronate/75 mL oral solution is equally bioavailable to the 70 mg alendronate oral tablet and the 35 mg alendronate/75 mL oral solution is not equally bioavailable to the 70 mg alendronate oral tablet.

An in-house search of ANDA submissions of alendronate sodium tablets indicated that generic firms had included both the 36-hour cumulative alendronate urinary excretion and maximum alendronate urinary excretion rate to assess bioequivalence between the 70 mg alendronate generic tablet and innovator tablet. The urine samples were collected predose, 0 - 0.5, 0.5 - 1, 1 - 2, 2 - 3, 3 - 4, 4 - 6, 6 - 8, 8 -12, 12 - 24, 24 - 36 h for measurement of excreted alendronate. Both rate and extent of alendronate urinary excretion have been used for determination of bioequivalence. An AB rating is granted to a generic drug product, if it is bioequivalent and pharmaceutically equivalent to the reference listed drug.

For Study P177, the sponsor collected predose, 0 - 8, 8 - 24, and 24 - 36 h urine samples to measure excreted alendronate. Assessment of maximum alendronate urinary excretion rate would not be reliable due to the long urine collection intervals. During the Optional Inter-Division Clinical Pharmacology Briefing for NDA 21-575, the participants would rather consider Study P177 as a bioavailability study and state that the 70 mg solution and 70 mg tablet are equally bioavailable based on the 36-hour cumulative alendronate urinary excretion. If demonstration of bioequivalence is the goal of a study, the sponsor should be advised to collect urine samples with intervals that are as short as possible to assess the maximum alendronate excretion rate in addition to the 36-hour cumulative alendronate excretion. However, the briefing participants raised the following concerns for the accuracy of estimating the maximum alendronate urinary excretion rate if the urinary collections were too frequent (e.g., half-an-hour interval) for initial few hours after dosing:

- the impracticality of voiding for urine collection
- the need to deliberately hydrate subjects and induce urination
- bioanalytical assay sensitivity to measure alendronate, especially for early samples

4. Did the sponsor adequately address dose linearity of oral solution from doses 70 mg/75 mL to 375 mg/100 mL?

Adequate. Per Dr. Michael J. Fossler's clinical pharmacology and biopharmaceutics review on June 30, 1995, the sponsor conducted a study (Protocol 17) in 15 postmenopausal women who received 5, 10, 40, or 80 mg alendronate tablets (see Attachment 3). The percent of alendronate dose excreted in urine over 36 hours postdose was similar at all doses, which indicated linear excretion from 5 – 80 mg.

The sponsor intends to market the 70 mg/75 mL oral solution. However, the sponsor conducted Study 204 to assess dose linearity and tolerability beyond 70 mg/75 mL

Study P204 was a 5-period, partially-blinded, placebo-controlled, single-rising-dose study in 25 healthy adults subjects (see synopsis in Attachment 4). Subjects received alendronate oral solution in 4 periods, at doses of 70 mg/75 mL, 140 mg/75 mL, 280 mg/75 mL, and 375 mg/100 mL in a rising-dose format and placebo in 1 period randomly interspersed in the treatment sequence following an overnight fast. Urine samples were collected over 36 hours postdose for alendronate determination.

Total Urinary Excretion of Alendronate* (µg) Over 36 Hours Following Administration of Each of 4 Single Oral Doses of Alendronate Oral Solution (Protocol 204) (N=25)

Dose	LS Mean	90% CI for LS Mean	LS Mean Dose Adjusted to 70 mg	90% CI for LS Mean Dose Adjusted to 70 mg
70 mg/75 mL	278.5	(235.7 - 329.1)	278.5	(235.7 - 329.1)
140 mg/75 mL	925.5	(783.3 - 1093.5)	462.7	(391.6 - 546.7)
280 mg/75 mL	2202.0	(1863.7 - 2601.7)	550.5	(465.9 - 650.4)
375 mg/100 mL	2527.4	(2139.1 - 2986.2)	471.8	(399.3 - 557.4)

* Data were back-transformed from log scale.
CI = Confidence interval.
LS = Least squares.

Total urinary excretion from 140 to 375 mg of alendronate oral solution indicates that urinary excretion exceeds dose-linearity between 70 and 140 mg and appears to increase dose-linearly between 140 and 375 mg. This is reflected in the differences in the LS mean total urinary excretion of alendronate, dose adjusted to 70 mg, at 70 mg versus the 140 to 375 mg doses in the table above. However, the total urinary excretion of alendronate following administration of the 70 mg/75 mL dose of the oral solution was generally similar to that seen in the previous studies of the 70 mg/75 mL oral solution, as indicated in the table below.

Total Urinary Excretion of Alendronate (µg) Over 36 Hours Following Administration of a Single 70 mg/75 mL Dose of Alendronate Oral Solution Across Protocols

Protocol	N†	LS Mean Total Urinary Excretion (µg)
163	12	288.4
177	108	293.6
204	25	278.5

† N = Number of subjects included in the analysis.
LS = Least squares.

5 Labeling Comments

The sponsor should change this statement to "FOSAMAX 70 mg oral buffered solution and FOSAMAX 70 mg tablet are equally bioavailable." from "

in the CLINICAL PHARMACOLOGY/*Absorption* section of the proposed labeling. See Attachment 5 for the complete proposed labeling.

Attachment 1

MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

MK-0217
Alendronate Sodium, Oral
[redacted] Solution
Osteoporosis

PROTOCOL TITLE/NO.: An Open-Label, Randomized, 5-Period, Crossover Study in Healthy Subjects to Determine the Bioavailability of Alternative Alendronate Oral Formulations Relative to the Marketed Tablet — #110

INVESTIGATOR/S/STUDY CENTER/S: [redacted]

PRIMARY THERAPY PERIOD: 01-Oct-1997 to 16-Jan-1998. The frozen file was achieved on 04-Jun-2002.

CLINICAL PHASE: V

DURATION OF TREATMENT: Five single doses of alendronate: a 10-mg marketed tablet, a 10-mg alendronate solution containing citrate buffer with [redacted] a 10-mg alendronate solution containing citrate buffer with combination sweetener, a 10-mg alendronate solution containing [redacted] buffer with combination sweetener, and 10-mg alendronate solution consisting of the components of the effervescent tablet formulation given as a solution (alendronate in citrate acid with [redacted]). A washout interval of approximately 7 days separated the doses. The duration of the study was approximately 8 weeks.

OBJECTIVE(S): (1) Estimation of the relative bioavailability of alendronate based on total urinary excretion from a 10-mg dose of alendronate, administered as each of 4 solutions, relative to the 10-mg marketed tablet. (2) Estimation of the within-subject variability measurements for total urinary excretion of alendronate when given as a solution versus a tablet. (3) Investigation of safety and tolerability of alendronate 10 mg administered as each of four solutions.

STUDY DESIGN: This was an open-label, randomized, single-dose, balanced, 5-period, crossover study in 20 healthy adult subjects. Subjects received 5 single doses of alendronate: the 10-mg marketed tablet and each of four 10-mg oral solutions. The components of the oral [redacted], solution in Treatments B, C, and D was reconstituted using sterile water and mixed to make a concentrated solution. Fifteen milliliters of the concentration was diluted to 75 mL using sterile water and administered to the subject. For Treatment E oral solution, the components of the effervescent tablet formulation was reconstituted using sterile water and mixed to a final volume of 135 mL and administered to the subject.

SUBJECT ACCOUNTING:

ENTERED: Total	21
Male (age range)	10 (18 to 41)
Female (age range)	11 (39 to 78)
COMPLETED:	19
DISCONTINUED: Total	2
Clinical adverse experience	0
Laboratory adverse experience	0
Treatment failure	0
Other	2 (protocol deviation, withdrew consent)

APPEARS THIS WAY ON ORIGINAL

DOSAGE/FORMULATION NOS.: Dosage and formulation numbers for Treatments A through E are as follows:

Dosage/Formulation Numbers--- Treatments A Through E

Drug	Potency	Formulation No.	Dosage Form	Dose Administered Following Reconstitution and Dilution[1]
Treatment A				
Alendronate Sodium	[redacted]	0217 OCT025F002	Marketed Tablet	--
Treatment B[2]				
MK-0217 Mono Sodium Trihydrate	[redacted]	0217 OPO001B001	Powder	[redacted]
[redacted]	[redacted]	0217 OPO002B001	Powder	[redacted]
Sodium Citrate, Dihydrate	[redacted]	0217 OPO003B001	Powder	[redacted]
Citric Acid, Anhydrous	[redacted]	0217 OPO004B001	Powder	[redacted]
Treatment C[4]				
MK-0217 Mono Sodium Trihydrate	[redacted]	0217 OPO001B001	Powder	[redacted]
Sodium Saccharin[5]	[redacted]	0217 OPO007B001	Powder	[redacted]
Sodium Citrate, Dihydrate	[redacted]	0217 OPO003B001	Powder	[redacted]
Citric Acid, Anhydrous	[redacted]	0217 OPO004B001	Powder	[redacted]
Treatment D[3]				
MK-0217 Mono Sodium Trihydrate	[redacted]	0217 OPO001B001	Powder	[redacted]
[redacted]	[redacted]	0217 OPO005B001	Powder	[redacted]
[redacted]	[redacted]	0217 OPO006B001	Powder	[redacted]
Sodium Saccharin[5]	[redacted]	0217 OPO008B001	Powder	[redacted]
Treatment E				
Alendronate Sodium	[redacted]	0217 EFT001F001	Powder	[redacted]
[redacted]	[redacted]	0217 EFT003F001	Granules	[redacted]
[redacted]	[redacted]	0217 EFT004F001	Powder	[redacted]
[redacted]	[redacted]	0217 EFT005F001	Powder	[redacted]
[redacted]	[redacted]	0217 EFT006F001	Powder	[redacted]
Citric Acid Anhydrous	[redacted]	0217 EFT002F001	Powder	[redacted]

[1] For Treatments B, C, and D, these doses are approximate as expected loss (minimal) likely occurred during reconstitution and dilution.
[2] Equivalent to 10 mg alendronate free acid.
[3] The components were combined to make a concentrated solution. This concentrated solution was diluted to the final dosing solution of 75 mL which contained 10 mg of alendronate free acid following reconstitution and dilution.
[4] [redacted] mono sodium trihydrate is approximately equivalent to 10 mg alendronate free acid in the final dosing solution of 75 mL.
[5] Sodium Saccharin represents the combination sweetener.
[6] Equivalent to 10 mg alendronate free acid in final dosing solution of 135 mL.

DIAGNOSIS/INCLUSION CRITERIA: Twenty male or nonpregnant female subjects, age 18 to 85 (males) and 36 to 85 (females), including at least 10 of each gender. The subjects were judged to be generally healthy based on medical history, physical examination, and laboratory safety studies.

EVALUATION CRITERIA: Urine for determination of total urinary excretion of alendronate was collected at -2 to 0 hours predose and 0 to 8, 8 to 24, and 24 to 36 hours postdose in each treatment period. Relative bioavailability was determined, using total urinary excretion, by the between-treatment comparisons for each of the 3 alternative 10-mg solution formulations and the alendronate effervescent tablet components in solution, versus the 10-mg marketed tablet. There were ninety percent confidence intervals (CI) calculated for the total urinary excretion geometric mean ratio (GMR) (10-mg alternative solution formulation/10-mg marketed tablet).

Safety and tolerability were assessed by vital signs, physical examination, electrocardiogram, laboratory safety tests, and adverse experience monitoring throughout the study.

STATISTICAL PLANNING AND ANALYSIS: The total urinary excretion of alendronate over 36 hours, following administration of each of the alternative 10-mg solution formulations and 10-mg marketed tablet, was analyzed using an analysis-of-variance model (ANOVA) appropriate for a 5-period, crossover design. The ANOVA model contained the factors: gender, subject within gender, period, and treatment. A log transformation was applied to the total urinary excretion data. The relative oral bioavailability using total urinary excretion of alendronate over 36 hours postdose was determined by constructing a 90% CI on the least-squares (LS) GMR between each of the alternative 10-mg formulations and the 10-mg marketed tablet. The 90% CIs were calculated using the Dunnett critical values. If the upper limit of the two-sided 90% CI for the GMR was <0.70 for any of the 10-mg alendronate solution formulations relative to the 10-mg alendronate marketed tablet, then it would be concluded that the absorption of alendronate, based on the total urinary excretion over 36 hours postdose, decreased by at least 30% for that solution formulation.

RESULTS:

PHARMACOKINETICS: The following table presents the summary statistics for the total urinary excretion of alendronate over 36 hours following administration of each of the alternative 10-mg solution formulations and the 10-mg marketed tablet.

Alendronate Formulation	Least-Squares (LS) Mean (µg) (90% CI[†])	Between-Subject SD[‡]	GMR[§]	90% CI of GMR	Posterior Probability[¶]
Treatment A (marketed tablet)	26.1 (22.5, 30.1)	36.5	--	--	--
Solutions					
Treatment B (citrate buffer and [redacted])	12.9 (11.1, 14.9)	18.1	0.49	(0.38, 0.65)	<0.001
Treatment C (citrate buffer and combination sweetener[¶])	26.6 (23.0, 30.7)	16.9	1.02	(0.78, 1.34)	0.909
Treatment D ([redacted] buffer and combination sweetener[¶])	13.3 (11.5, 15.4)	15.8	0.51	(0.39, 0.67)	0.001
Treatment E (components of effervescent tablet)	25.9 (22.4, 30.0)	21.3	0.99	(0.76, 1.31)	0.911

† Confidence interval (using the Dunnett corrected critical value).
‡ SD = Standard deviation (back-transformed from the natural log scale).
§ Geometric Mean Ratio = LS mean of alternative formulation/LS mean of marketed tablet.
¶ Probability that the true GMR is within the bioequivalence bounds of (0.80 and 1.25).
¶ Combination sweetener contained saccharin.

The between subject standard deviations for Treatments A (marketed tablet), B (alendronate in citrate buffer with [redacted] C (alendronate in citrate buffer with combination sweetener), D (alendronate in [redacted] buffer with combination sweetener), and E (effervescent tablet components in solution) were 36.5, 18.1, 16.9, 15.8, and 21.3 µg, respectively. The between-subject standard deviation (its corresponding 95% CI) in log scale for Treatments A (marketed tablet), B (alendronate in citrate [redacted] with [redacted] C (alendronate in citrate buffer with combination sweetener), D (alendronate in [redacted] buffer with combination sweetener), and E (effervescent tablet components in solution) were 0.82 (0.65, 1.14), 0.82 (0.65, 1.14), 0.51 (0.40, 0.71), 0.76 (0.60, 1.05), and 0.61 (0.48, 0.85) ln µg, respectively. Overall, the within-subject variability (root mean square error, RMSE) and its 90% CI was 0.38 (0.33, 044) ln µg.

The LS mean values for total urinary excretion of alendronate were similar following administration of 10-mg alendronate given as Treatments A (marketed tablet), C (alendronate in citrate buffer with combination sweetener), and E (effervescent tablet). Treatments B (alendronate in citrate buffer with [redacted] and D (alendronate in [redacted] buffer with combination sweetener) exhibited relatively lower alendronate LS mean values for total urinary excretion.

The point estimates of the LS GMR of both Treatments B and D with respect to the marketed tablet were lower than 0.70. Examination of the 90% CI revealed that for Treatments B and D, the upper limit of the 90% CI for the GMR with respect to the marketed tablet was lower than the predefined limit (<0.70). Therefore, the absorption of alendronate, based on total urinary excretion of alendronate over 36 hours postdose, decreased by at least 30% for Treatments B (alendronate in citrate buffer with [redacted] and D (alendronate in [redacted] buffer with combination sweetener) relative to the 10-mg alendronate marketed tablet.

The posterior probabilities that the true GMR is within bioequivalence bounds of (0.80, 1.25) for GMRs of Treatments B, C, D, and E with respect to the marketed tablet were <0.001, 0.909, 0.001, and 0.911, respectively.

SAFETY: All 21 study participants were included in the safety analysis. Eleven subjects reported a total of 24 clinical adverse experiences, 5 of which (all occurring in 1 subject) were considered serious. The most common adverse experience was headache (10 episodes reported by 6 subjects). Fifteen of 24 clinical adverse experiences were mild and 21 were judged to be probably not or definitely not drug related. Three of the 24 clinical adverse experiences were considered possibly drug related by the investigator. One subject (AN 019) had nausea and vomiting of moderate intensity and another subject (AN 009) had a headache of mild intensity.

The 5 serious clinical adverse experiences were atrial fibrillation, supraventricular tachycardia, lung mass, congestive heart failure, and bibasilar pleural effusions. All were judged to be consistent with worsening of a preexisting condition and of severe intensity. The subject had a history of bilateral pleural effusions, lung mass, atelectasis, and congestive heart failure, diagnosed approximately 3 months prior to study start but not known to the investigator prior to the serious clinical adverse experiences. The subject had received 3 single doses of alendronate (Treatments A, E, and B), each separated by at least 7 days. The subject had been discharged from the clinic following the third dose and presented to the emergency department complaining of shortness of breath, palpitations, weakness, and diaphoresis. The most recent dose of alendronate was administered one day prior to these symptoms. The subject was subsequently hospitalized for 5 days, during which his symptoms were brought under control and numerous diagnostic tests were performed. These tests indicated that the lung mass was not malignant, and that the causes of the subject's presenting symptoms were consistent with the diagnoses listed above. Following discharge, the subject continued in the study, receiving the final 2 single doses of alendronate. The investigator rated these serious adverse experiences as definitely not drug related.

There were 3 laboratory adverse experiences in 2 subjects, which consisted of increased leukocytes in 1 subject and 2 episodes of increased urinary leukocytes in another subject. These were judged to be probably not and definitely not drug related, respectively. There were no serious laboratory adverse experiences.

CONCLUSIONS: (1) The relative bioavailabilities of alendronate in both Treatment C (10 mg/75 mL alendronate solution with citrate buffer and combination sweetener) and Treatment E (comprised of components of an effervescent tablet) are generally similar to that of the 10-mg marketed tablet, and [redacted] (2) The relative bioavailabilities of alendronate in the 10-mg alternative solution formulations, consisting either of citrate buffer and [redacted] (Treatment B) or [redacted] buffer and combination sweetener (Treatment D), are significantly less than that of the 10-mg marketed tablet, and [redacted] (3) Alendronate, administered as single doses of 10-mg of each of the 4 alternative solutions, is generally well tolerated and has a favorable safety profile.

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MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

MK-0217
Alendronate Sodium, Oral
[redacted] Solution and Tablet
Osteoporosis

PROTOCOL TITLE/NO.: An Open-Label, Randomized, 3-Period, Crossover, Pilot Study to Examine the Relative Bioavailability of an Oral [redacted] Alendronate Solution in Healthy Adult Subjects #163

INVESTIGATOR/STUDY CENTER: [redacted]

PRIMARY THERAPY PERIOD: 20-May-2000 to 17-Jun-2000. The frozen file was achieved on 27-Jun-2001. **CLINICAL PHASE:** V

DURATION OF TREATMENT: Three single doses of alendronate: a 35-mg or 70-mg oral [redacted] solution and a 70-mg oral tablet. A washout interval of 13 days separated the doses. The duration of the study was approximately 6 weeks.

OBJECTIVES: (1) To examine the relative urinary excretion of alendronate 70 mg given as an oral [redacted] solution compared with that observed with the alendronate 70-mg tablet. (2) To examine the relative urinary excretion of alendronate 35 mg given as an oral [redacted] solution compared with that observed with the alendronate 70-mg tablet.

STUDY DESIGN: This was an open-label, randomized, 3-period, balanced, crossover study conducted in 12 healthy adult subjects. Subjects received 3 single doses of alendronate: the 35-mg and 70-mg oral [redacted] solution and the 70-mg tablet. A washout interval of 13 days separated the doses.

SUBJECT ACCOUNTING:

ENTERED: Total	12
Male (age range, years)	7 (35 to 73)
Female (age range, years)	5 (30 to 62)
COMPLETED:	12
DISCONTINUED: Total	0
Clinical adverse experience	0
Laboratory adverse experience	0

DOSAGE/FORMULATION NOS.: Alendronate 35-mg/75-mL oral [redacted] solution: Formulation No. 0217 OSO001F001; Alendronate 70-mg/75-mL oral [redacted] solution: Formulation No. 0217 OSO013B001; Alendronate 70-mg oral tablet: Formulation No. 0217 OCT001J005.

DIAGNOSIS/INCLUSION CRITERIA: Twelve male or nonpregnant female subjects, age 18 to 85, including at least 4 of each gender. At least 6 of the subjects were 50 years of age or older. The subjects were judged to be generally healthy based on medical history, physical examination, and laboratory safety studies.

EVALUATION CRITERIA: Total urinary excretion of alendronate was determined over a 36-hour period following single-dose administration of a 35-mg or 70-mg oral [redacted] solution and a 70-mg oral tablet dose. Relative bioavailability was estimated from the individual urinary excretions. Safety and tolerability were assessed prestudy and poststudy by vital signs, physical examinations, laboratory safety tests, and adverse experience monitoring throughout the study.

STATISTICAL PLANNING AND ANALYSIS: Comparisons of the dose-adjusted (to 70 mg) total urinary excretion for the 35-mg and 70-mg [redacted] solutions relative to the 70-mg oral tablet were performed using an analysis of variance (ANOVA) model suitable for a 3-period, crossover design. The ANOVA model contained factors for subject, period, and treatment. Presence of a carryover effect was tested and found to be not significant. Total urinary excretion was log transformed. To estimate the relative bioavailability for each of the [redacted] solution dose (35 mg and 70 mg) versus the 70-mg tablet, a 95% confidence interval (CI) on the dose-adjusted geometric mean ratio (GMR) for total urinary excretion was calculated.

RESULTS:

PHARMACOKINETICS: The dose-adjusted alendronate total urinary excretion GMRs and 95% CIs were 1.15 (0.78, 1.70) for the 35-mg ——— solution/70-mg tablet and 1.08 (0.73, 1.59) for the 70-mg '———solution/70-mg tablet.

SAFETY: All 12 study participants were included in the safety analysis. No serious clinical adverse experiences were reported. Five subjects reported a total of 13 clinical adverse experiences. The most common adverse experience was headache (5 episodes reported by 3 subjects). All but one of the clinical adverse experiences were mild. There were no laboratory adverse experiences reported

CONCLUSIONS: (1) The relative bioavailability of alendronate in the 35-mg and 70-mg oral solution is generally similar to that of the 70-mg tablet, with estimated geometric mean ratios of 1.15 and 1.08 for the 35-mg and 70-mg oral '———' solution, respectively, relative to that of the 70-mg tablet. (2) Alendronate, administered as single doses of the 35-mg and 70-mg oral ——— solutions in 75 mL or as the 70-mg tablet, is generally well tolerated and has a favorable safety profile.

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Attachment 2

Study P177 had 2 stages. Since they observed equal bioavailability between the 70 mg solution and 70 mg tablet in Stage 1, they did not proceed to Stage 2 of Study P177. The sponsor did not initially elaborate on how the 93.5% CI was chosen for both Stage I and Stage II of the study in order to preserve an overall 5% type I error rate for the study. For this reason, this reviewer used the more conservative 99% CI and 95% CI approach to confirm equal bioavailability besides the 90% CI (see SAS codes and outputs below). Through the sponsor's SAS transport files submitted on July 18, 2003 (N000BZ), this reviewer reproduced the same geometric mean ratio (GMR) and 93.5% CI for the 70 mg solution versus 70 mg tablet and the same GMR and 90% CI for the 35 mg solution versus 70 mg tablet as reported by the sponsor.

Summary statistics to assess BE follows:

70 mg alendronate	GMR	90% CI	93.5% CI	95% CI	99% CI
solution vs. tablet	0.9945	0.8987 – 1.100	0.8876 – 1.114	0.8812 – 1.122	0.8479 – 1.166
(mg) alendronate	GMR	90% CI	93.5% CI	95% CI	99% CI
(35) solution vs. (70) tablet	0.8378	0.7563 – 0.9282	0.7468 – 0.9399	0.7415 – 0.9467	0.7132 – 0.9843

Based on these observations, the 70 mg alendronate/75 mL oral solution is equally bioavailable to the 70 mg alendronate oral tablet and the 35 mg alendronate/75 mL oral solution is not equally bioavailable to the 70 mg alendronate oral tablet.

This reviewer does not intend to establish new criteria or policy to determine bioequivalence, which is the Office of Pharmaceutical Science's responsibility. The different % CI calculations were for reference to this reviewer.

Upon request, the sponsor submitted the following response on August 14, 2003 via e-mail and official copy NDA 21-575 N000BB on August 25, 2003 for:

MK-0217 NDA 21-575 August 4, 2003 FDA Query
Protocol #177:
Definitive Bioequivalence Study of the 70-mg Oral ——— Solution and 70-mg Oral tablet

FDA Questions:

Question 1: Please provide the statistical formula you used to determine that 93.5% confidence interval for the geometric mean ratio of 70 mg solution to 70 mg tablet was appropriate for the two-stage test.

Question 2: Please provide the statistical formula you used to calculate the number of subjects needed for Stage 2 (should the study have proceeded to Stage 2).

MRL Response:

A two-stage approach for bioequivalence testing is useful when a considerable amount of uncertainty exists about the true state of nature (i.e., how far the true but unknown underlying formulations deviate from each other as well as the true but unknown variance estimates). If the geometric mean ratio

(GMR) of the pharmacokinetic parameter (in this case the total urinary excretion of alendronate) of the two formulations deviates from unity by a small amount (but still within the bioequivalence tolerance limits of (0.80, 1.25)) the power of the statistical test can decrease dramatically. In such situations single stage tests are unlikely to be successful in demonstrating bioequivalence unless the sample size is excessively large. A two-stage approach offers the opportunity of more efficient decision making and the possibility of minimizing the overall number of study subjects unnecessarily treated by allowing earlier abandonment of lost causes: i.e., when Stage 1 results indicate clinically important differences in the formulations.

Since the answers to both questions 1 and 2 are interlinked, the response below addresses both of the questions. Note that given the bioequivalence result from Stage 1 of Protocol #177, it was not necessary to conduct Stage 2.

For this two-stage design no explicit formula was used to develop the Stage 1 confidence interval calculation, rather a joint clinical and statistical judgment was employed in selecting the parameters of this two-stage design. Simulations were then performed to ensure that the overall type I error rate was at the nominal 5% level. In this particular study, for simplicity the prespecified confidence interval was chosen to be roughly equal (93.5%) at both Stages 1 and 2 with the proposed sample sizes (108 in Stage-1 and 126 in Stage-2) should the trial proceed to Stage-2 and still satisfy the condition for the overall type I error-rate on the entire trial at the nominal 5% level given the data available at the design stage. At the design stage the choice of a sample size of n=108 yielded approximately 80% probability to show bioequivalence given that the true ratio between formulations was 1.00 and approximately 50% probability power to claim bioequivalence for the case where the true ratio was 1.10, as was approximately observed in the initial pilot study (Clinical Study Report for Protocol #163 (GMR was ~1.10)).

Note since the two-stage design reached a decision criteria at Stage 1 there was no need to compute an actual Stage 2 sample size. The procedure allows one to incorporate Stage 1 information in updating parameter estimates and to compute a Stage 2 sample size while still preserving the overall type I error rate at 0.05. An example of this process is as follows: If following Stage 1 it was felt that the true ratio was still 1.10 but the Root Mean Square Error (RMSE) had increased to 0.50, a sample size of n=126 in Stage 2 would have provided approximately 80% power using a 93.5% confidence interval. Other Stage 2 sample sizes would be derived based on other scenarios. In all of these cases, the type I error rate would be protected. Table 1 of the attached memo (Appendix I , Page 5), verifies that the choices of confidence coefficients and sample sizes yielded a 5% type-I error rate for some other reasonable values of Root Mean Square Error (RMSE) as prespecified in Protocol #177. Note that from Stage 1 of Protocol #177 the observed RMSE was 0.45.

In this table the specific supportive parameters of the two-stage design for a stopping rule as described in Protocol #177 are presented. The prespecified interval bound used here is $(-\Delta, \Delta) = (-0.223, 0.223)$ which corresponds to the 20% bound in the log-scale; i.e. (0.80, 1.25) in the original scale. The sample sizes required at both stages increases as the true log-GMR (denoted as θ) gets further away from zero. Here we consider $\theta = 0.0953 \approx \log(1.1)$ which allows the true means to be as far as 10% apart from each other. Consequently, to allow greater variability in the observed GMR estimate at stage 1, we used $Dx = 0.1823 \approx \log(1.2)$, where Dx is defined a priori at the design stage and is the cut-off of the

observed GMR in Stage I such that too many resources would have been required to show bioequivalence (if at all) of the two formulations. We used n_1=108 (Stage-1 sample size), and n_2 = 126 (Stage-2 sample size) for purposes of illustration. Different values of Root Mean Square Error (RMSE) in the log scale from 0.45 up to 0.50 are considered to illustrate the impact on the design parameters including the overall power, type-I error rate, and the probability of continuing the trial to the second stage, etc. The results are obtained by simulation of 1,000,000 studies using a C++ programming code. The reported values are rounded up to 3 decimal places.

Further details describing the overall statistical properties, motivation, and derivations of this two-stage design bioequivalence design methodology can be found in a more comprehensive technical report provided in Appendix II. Since the proposed sample sizes were large, one can also use Result 1 of this appendix to check and compute the type-I error rate for those sample size choices (as discussed in Remark 3 of Section 4.1: Appendix II). A subset of this material was recently presented at the Joint Statistical Meeting of the American Statistical Association (ASA) in August of this year. Theoretical results supported with extensive simulations from the technical report were used to establish and verify the appropriateness of the above parametric and methodological choices used in this study.

In summary, both the theoretical work and extensive simulation results support that the use of the 93.5% CIs properly controls the overall type I error rate in this two-stage design with the given sample sizes.

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CLINICAL STUDY REPORT
I. SYNOPSIS

MK-0217
Alendronate Sodium, Tablet,
[redacted] Solution
Osteoporosis

PROTOCOL TITLE/NO.: An Open-Label, Randomized, 2-Stage, 3-Period, Crossover Study to Evaluate the Bioequivalence of 35-mg and 70-mg Oral [redacted] Alendronate Solutions to a 70-mg Alendronate Tablet in Healthy Adult Subjects #177

INVESTIGATOR(S)/STUDY CENTER(S): [redacted]

PRIMARY THERAPY PERIOD: 04-Nov-2000 to 17-Mar-2001. Frozen file was achieved on 01-May-2002. **CLINICAL PHASE:** V

DURATION OF TREATMENT: Three single doses of alendronate: a 70-mg oral tablet, a 35-mg oral [redacted] solution, and a 70-mg oral [redacted] solution. A washout interval of at least 12 days separated the doses. The duration of the treatment was approximately 5 weeks.

OBJECTIVE(S): Primary: To compare the urinary excretion of alendronate following a 70-mg alendronate oral [redacted] solution to that observed following an alendronate 70-mg tablet. Secondary: To compare the urinary excretion of alendronate following a 35-mg alendronate oral [redacted] solution to that observed following an alendronate 70-mg tablet.

STUDY DESIGN: This was an open, randomized, 3-period, 2-stage, balanced, crossover study in 108 healthy adult subjects. Subjects received 3 single doses of alendronate: a 70-mg tablet, a 70-mg oral [redacted] solution, and a 35-mg oral [redacted] solution. A washout interval of at least 12 days separated the doses. Based on the primary endpoint, only 1 stage was conducted.

SUBJECT ACCOUNTING:

ENTERED: Total	115
Male (age range)	55 (18 to 79)
Female (age range)	60 (18 to 77)
COMPLETED (per protocol):	106
COMPLETED (for primary analysis):	108
DISCONTINUED: Total	9
Clinical adverse experience	2
Laboratory adverse experience	0
Other	7 (3 withdrew consent, 3 lost to follow-up, 1 violated clinic rules of conduct)

DOSAGE/FORMULATION NOS.:

Batch No.	Dose	Alendronate Form	Formulation No.
Clinical Supplies			
WP-H804	70 mg	Tablet	0217 OCT001J009
WP-H805	35 mg/75 mL	[redacted] Solution	0217 OSO003F002
WP-H806	70 mg/75 mL	[redacted] Solution	0217 OSO015B002
Retention Supplies			
WP-H804A	70 mg	Tablet	0217 OCT001J009
WP-H805A	35 mg/75 mL	[redacted] Solution	0217 OSO003F002
WP-H806A	70 mg/75 mL	[redacted] Solution	0217 OSO015B002

DIAGNOSIS/INCLUSION CRITERIA: One hundred eight male or nonpregnant female subjects, ages 18 to 85. The subjects were judged to be generally healthy based on medical history, physical examination, and laboratory safety studies.

EVALUATION CRITERIA: Relative bioavailability of alendronate was determined by the between-treatment comparison of 70-mg oral ——— solution versus the 70-mg tablet, and the 35-mg oral ——— solution (dose adjusted to 70 mg) versus the 70-mg tablet, using total urinary excretion of alendronate over 36 hours. Confidence intervals (CI), 95.5% and 90%, were calculated for the total urinary excretion geometric mean ratio (GMR) of 70-mg solution and 35-mg solution (dose adjusted to 70 mg) with respect to 70-mg tablet, respectively. Urine for each treatment period was collected at -2 to 0 hours predose, 0 to 8, 8 to 24, and 24 to 36 hours postdose on Days 1 and 2.

STATISTICAL PLANNING AND ANALYSIS: A 2-stage design, 3-period, balanced, crossover study was conducted to assess the relative bioavailability of 70-mg oral ——— solution and 35-mg oral ——— solution with respect to the 70-mg tablet, using the total urinary excretion of alendronate over 36 hours after single-dose administration of each of the formulations. This 2-stage design sequential study was predefined by a stopping rule based on the observed least-squares (LS) GMR of the 70-mg solution and 70-mg tablet and its 93.5% CI. The decision rule to proceed to Stage 2 was based solely on the comparison of the 70-mg solution with the 70-mg tablet. Bioequivalence of the 70-mg oral ——— solution with the 70-mg tablet was concluded if the 93.5% CI of the GMR (70-mg solution/70-mg tablet) was contained within the prespecified comparability limits of ——— following Stages 1 or 2 of the sequential design.

In Stage 1 of the sequential design, the total urinary excretion of alendronate over 36 hours following administration of the 70-mg solution, 35-mg solution, and 70-mg tablet was analyzed using an analysis of variance model (ANOVA) appropriate for a 3-period crossover design. The ANOVA model contained, as factors, subject, period, and treatment. A natural log transformation was applied to the total urinary excretion data. Bioequivalence of the 70-mg oral ——— solution to the 70-mg tablet was concluded if the 93.5% CI of the GMR (70-mg solution/70-mg tablet) was contained within the prespecified comparability limits of ——— following Stage 1. Since the comparison of the 35-mg solution to the 70-mg tablet was secondary, the decision rule to proceed to Stage 2 was not based on this comparison. If the study was stopped after Stage 1, bioequivalence of the 35-mg oral ——— solution (dose adjusted to 70 mg) to the 70-mg tablet would be concluded if the 90% CI of the GMR of 35-mg solution (dose adjusted to 70 mg)/70-mg tablet was contained within the prespecified bounds of ——— following Stage 1 of the sequential design.

RESULTS:

PHARMACOKINETICS: At Stage 1, the point estimates of the GMR of 70-mg solution and 35-mg solution (dose adjusted to 70 mg) with respect to the 70-mg tablet were 0.99 and 0.84, respectively, following Stage 1.

Note that based on the results from Stage 1, Stage 2 was not conducted.

The 93.5% CI of the GMR for the 70-mg solution with respect to the 70-mg tablet was (0.89, 1.11), which fell within the prespecified bioequivalence bounds of ———. Thus, the 70-mg solution is bioequivalent to the 70-mg tablet. Since the 93.5% CI for GMR of the 70-mg solution with respect to the 70-mg tablet met the predefined acceptance criteria for stopping the study following Stage 1, Stage 2 of the design was not conducted. The 90% CI of the GMR for the 35-mg solution (dose adjusted to 70 mg) with respect to the 70-mg tablet was (0.76, 0.93) which fell slightly outside the prespecified bioequivalence bounds of ———. The 35-mg oral ——— solution (dose adjusted to 70-mg) exhibited relatively lower alendronate LS mean values for total urinary excretion ($p=0.005$) compared with the 70-mg tablet.

The following table presents the summary statistics for the total urinary excretion of alendronate (µg) over 36 hours following administration of the 70-mg tablet, 70-mg oral ——— solution, and dose-adjusted 35-mg oral ——— solution.

Treatment	Least-Squares (LS) Geometric Mean (90% CI)[1]	GMR[2]	CI of GMR[3]	p-Value[4]
70-mg tablet	295.27 (274.86, 317.19)			
70-mg oral [redacted] solution	293.63 (273.34, 315.44)	0.99	(0.89, 1.11)	0.928
35-mg oral [redacted] solution	247.38 (229.93, 266.16)	0.84	(0.76, 0.93)	0.005

[4] p-Value relative to the 70-mg tablet.
[1] Back-transformed from log scale obtained from ANOVA.
[2] Geometric Mean Ratio (GMR) = Least-squares (LS) geometric mean of solution/LS geometric mean of tablet.
[3] 91.5% CI of GMR (70-mg solution/70-mg tablet), 90% CI of GMR (dose-adjusted 35-mg solution/70-mg tablet).

SAFETY: All 115 study participants were included in the safety analysis. Sixty-six subjects reported a total of 219 clinical adverse experiences. Twenty-six subjects reported at least 1 adverse experience which was considered by the investigator to be drug related, while all adverse experiences were considered non-drug-related in 40 subjects. Clinical adverse experiences were generally similarly distributed among the 3 treatments. The most common drug-related adverse experiences were headache (reported by 2 subjects following the 70-mg tablet, 4 following the 70-mg solution, and 2 following the 35-mg solution), diarrhea (2 following the 70-mg tablet, 3 following the 70-mg solution, and 2 following the 35-mg solution), and nausea (2 following the 70-mg tablet, 1 following the 70-mg solution, and 3 following the 35-mg solution). No laboratory adverse experiences were reported.

One subject reported a serious adverse experience consisting of viral gastroenteritis, which was considered by the investigator to be probably not related to study drug. This subject experienced gastrointestinal and flu-like symptoms beginning several hours following his initial dose of alendronate, and was sent by the investigator to an emergency department the morning of Day 2 when the severity of the symptoms increased. In the emergency department, the subject was diagnosed with viral gastroenteritis and was treated with ibuprofen and intravenous fluids. The subject was discontinued from the study.

In addition, one subject was discontinued from the study for a clinical adverse experience of hives, which developed after completion of the second study period

CONCLUSIONS: (1) The 70-mg alendronate oral buffered solution is bioequivalent to the 70-mg alendronate marketed tablet. (2) The GMR (90% CI) for the 35-mg alendronate oral [redacted] solution, dose adjusted to 70 mg, relative to the 70-mg alendronate marketed tablet, is 0.84 (0.76, 0.93), with the lower bound slightly outside the bioequivalence limit. (3) Alendronate, administered as single doses of the 35-mg and 70-mg oral [redacted] solutions in 75 mL or as the 70-mg tablet, is generally well tolerated and has a favorable safety profile.

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20 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Attachment 3

IV. Dose and Dosage Form Proportionality

Alendronate will be available in 10 and 40 mg tablets. The recommended dose is 10 mg daily for post-menopausal osteoporosis and 40 mg daily for Paget's disease of bone.

A study in 15 post-menopausal women given 5, 10, 40 or 80 mg tablets of alendronate in a crossover fashion was performed to assess dose linearity. The percent of dose excreted in the urine over 36 hours is similar at all doses (Table 4).

Table 4: Mean total urinary excretion (std dev, cv%) and % dose excreted over 36 hours in 15 post-menopausal women given 5-80 mg alendronate orally. The results indicate linear excretion from 5-80 mg. (Protocol 17)

Dose (mg)	Total excretion over 36 hrs (μg)	Percent of dose excreted over 36 hours
5	18.6 (14.0, 75.3%)	0.395
10	43.6 (31.6, 72.5%)	0.446
40	170.9 (105.4, 61.7%)	0.429
80	355.4 (366.4, 103%)	0.437

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Attachment 4

MERCK RESEARCH LABORATORIES

CLINICAL STUDY REPORT
I. SYNOPSIS

MK-0217
Alendronate Sodium, Oral
———Solution
Osteoporosis

PROTOCOL TITLE/NO.: A 5-Period, Partially-Blinded, Placebo-Controlled, Single-Rising-Dose Study to Measure the Safety, Tolerability, and Dose Proportionality of Alendronate Oral Solution in Healthy Volunteers #204

INVESTIGATOR(S)/STUDY CENTER(S):

PRIMARY THERAPY PERIOD: 20-Aug-2001 to 17-Nov-2001
The frozen file was achieved on 01-May-2002.

CLINICAL PHASE: V

DURATION OF TREATMENT: Four single doses of alendronate oral ——— solution, 70 mg/75 mL, 140 mg/75 mL, 280 mg/75 mL, and 375 mg/100 mL, and a single dose of placebo in either 75-mL or 100-mL solution. A washout interval of approximately 2 weeks separated the doses. The duration of the study was approximately 14 weeks.

OBJECTIVE(S): (1) To determine the safety and tolerability of alendronate oral ——— solution at doses of 70, 140, 280, and 375 mg. (2) To examine the relative urinary excretion of alendronate following oral doses of 70, 140, 280, and 375 mg administered as an oral——— solution.

STUDY DESIGN: This was a 5-period, partially-blinded, placebo-controlled, single-rising-dose study in 25 healthy adults subjects. Subjects received alendronate oral solution in 4 periods, at doses of 70, 140, 280, and 375 mg in a rising-dose format and placebo in one period randomly interspersed in the treatment sequence following an overnight fast. Urine was collected over 36 hours following each dose for alendronate determination.

SUBJECT ACCOUNTING:

ENTERED: Total	30
Male (age range)	13 (23 to 65)
Female (age range)	17 (20 to 59)
COMPLETED:	25
DISCONTINUED: Total	5
Clinical adverse experience	0
Laboratory adverse experience	0
Other	5 (withdrew consent)

DOSAGE/FORMULATION NOS.: Treatment A: alendronate 70-mg/75-mL oral ——— solution, Formulation No 0217 OSO020B003; Treatment B: alendronate 140-mg/75-mL oral ——— solution, Formulation No. 0217 OSO021I001; Treatment C: alendronate 280-mg/75-mL oral ——— solution. Formulation No.: 0217 OSO022G001; Treatment D: alendronate ~375-mg/100-mL oral ——— solution, Formulation No. 0217 OSO022G001 (same formulation as Treatment C using a larger dosage volume); Treatment E: placebo for alendronate oral ——— solution, Formulation No.: P0217 OSO017P003.

DIAGNOSIS/INCLUSION CRITERIA: Twenty-five nonpregnant females or male subjects between the ages of 18 and 65. The subjects were judged to be healthy based on medical history, physical examination, and laboratory safety studies.

EVALUATION CRITERIA: Safety and tolerability were assessed by vital signs, laboratory safety tests, and adverse experience monitoring throughout the study. The dose proportionality of alendronate with respect to the total urinary excretion over 36 hours postdose, following single-dose administration of 70-, 140-, 280-, and 375-mg oral ——— solutions, was assessed by a power law regression model. A 90% confidence interval (CI) for the slope was calculated based on the methodology proposed by ———. Additionally, pairwise comparisons of the geometric mean total urinary excretion of alendronate for each of the dose levels (dose adjusted to 70 mg) were evaluated for significant differences among doses. Urine for each treatment period was collected at ~2 to 0 hours predose and at 0 to 8, 8 to 24, and 24 to 36 hours postdose on Day 1 and Day 2 in each period.

STATISTICAL PLANNING AND ANALYSIS: Dose proportionality was assessed in 2 steps: first by the power-law model and second by a pairwise comparison of geometric means of total urinary excretion of alendronate among the doses (dose adjusted to 70 mg). For the power law model, natural log (ln) of total urinary excretion of alendronate was modeled as a function of subject and ln (dose). Dose proportionality over the entire dose range of 70 to 375 mg would be concluded if the 90% CI for the slope of ln (total urinary excretion of alendronate) versus ln (dose), computed from the linear regression model, fell within the interval of ———. These limits for the slope criteria were based on a pairwise comparison for the 90% CI of the dose-adjusted geometric mean ratio (GMR) falling within 33% or ——. Linearity was tested by adding a quadratic term for ln (dose) and examining its significance. In the second step, an analysis of variance (ANOVA) model appropriate for a 5-period, rising-dose design was selected. In addition, a pairwise comparison between the 375 mg and 70 mg was also computed using the ANOVA model. Pairwise comparisons of geometric mean total urinary excretion of alendronate for each of the doses (adjusted to 70 mg) and 70 mg were also evaluated. The 90% CIs for the pairwise comparisons between the dose levels were generated from the ANOVA model, based upon the t-distribution. Since both slope criteria and the pairwise comparisons indicated that 70-mg dose significantly differed from the higher doses (dose adjusted to 70 mg), a step-up procedure was implemented in which the 70-mg dose was excluded and the power-law model was refitted to the remaining doses, and the above procedures were repeated. Dose proportionality over the dose range of 140 to 375 mg would be concluded if the 90% CI for the slope of ln (total urinary excretion of alendronate) versus ln (dose), computed from the linear regression model, fell within the interval ——. This interval reflected the 2.68-fold increase over the remaining dose range of 140 to 375 mg, and was derived using the ±33% pairwise criteria as outlined in ——.

RESULTS:

PHARMACOKINETICS: The least-squares (geometric) means for total urinary excretion of alendronate, dose-adjusted to 70 mg, were 278.5, 462.7, 550.5, and 471.8 µg for the 70-, 140-, 280-, and 375-mg doses, respectively. The relative urinary excretion following the 70-mg oral —— solution was generally similar to previous studies of the 70-mg oral ——, solution.

Dose proportionality was not observed for total urinary excretion of alendronate over the entire dose range, 70 to 375 mg. The slope and 90% CI for the entire dose range, obtained from the power law model, was 1.34 (——), which did not meet the prespecified criteria ——. The quadratic term (to examine lack of fit), when added to the model, was found to be significant, indicating that the first-order model did not fit the data.

Statistically significant differences were observed for the pairwise comparisons of the geometric means between 70 mg alendronate and all of the higher doses (dose adjusted to 70 mg) ($p<0.001$). The dose adjusted GMR (375 mg/70 mg) was 1.69 with a 90% CI of (1.34, 2.14). Hence, based on the power-law model and the pairwise comparisons, dose proportionality may not be claimed for total urinary excretion of alendronate over the entire dose range of 70 to 375 mg.

Since the power-law model fitted with all the doses from 70 to 375 mg did not meet the predefined slope criteria and failed the linearity test, indicating that the dose-adjusted total urinary excretion of alendronate at the 70-mg dose was significantly different from the higher doses, a step-up procedure was implemented in which the 70-mg dose was dropped and the power-law model refitted. The slope and the 90% CI for the dose range 140 to 375 mg was 1.06 (——), which was within the prespecified criteria ——. The quadratic term, when added to the model, was found to be nonsignificant, indicating that the linear model fit the data. In addition, the dose-adjusted GMR between the 140-mg and 375-mg doses was 1.02, with a 90% CI of (0.81, 1.29), that fell within the prespecified comparability interval of ——. Therefore, since both the slope criteria and the pairwise criteria were satisfied, dose proportionality could be claimed for the total urinary excretion of alendronate over the dose range 140 to 375 mg.

SAFETY: Twenty-three subjects reported a total of 94 clinical adverse experiences. Forty-seven (49%) of the clinical adverse experiences were considered by the investigator to be drug related. The most common drug-related clinical adverse experiences overall were headache (12 episodes), musculoskeletal pain (10 episodes), fever (4 episodes), and diarrhea (6 episodes). Forty-one of the 47 drug-related clinical adverse experiences were considered mild. Moderate drug-related clinical adverse experiences consisted of abdominal pain, diarrhea, and headache in one subject at 375 mg, diarrhea in one subject at 280 mg, bone pain in one subject at 70 mg, and myalgia in one subject at 70 mg. The percentage of subjects with at least one drug-related clinical adverse experiences at each dose level was 0, 26.7, 11.1, 24, and 16% for placebo, 70, 140, 280, and 375 mg alendronate, respectively.

One subject reported a serious clinical adverse experience consisting of an elective termination of pregnancy. This subject had a negative urine pregnancy test prior to each of the 5 dosing periods. At her poststudy visit, a serum pregnancy test was positive and the subject indicated that she took emergency contraception 4 days following study drug administration in Period 5 (375 mg alendronate). Thirty-one days following her last dose of study drug, she electively terminated her pregnancy. The estimated gestational age at termination was 7 weeks. No study participant discontinued treatment due to a clinical adverse experience, and no study participant died during the study. There were no laboratory adverse experiences in any subject.

CONCLUSIONS: (1) Single doses of 70-, 140-, 280-, and 375-mg alendronate oral [redacted] solution are generally well tolerated and have a favorable safety profile. (2) The relative urinary excretion following administration of 70 mg alendronate is generally similar to values observed in previous studies of the oral buffered solution. (3) The relative urinary excretion of alendronate is not dose proportional within the dose range 70 to 375 mg but is dose proportional within the dose range 140 to 375 mg.

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